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Signed Stephen Hurdle

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1/77

Request for grant of a patent

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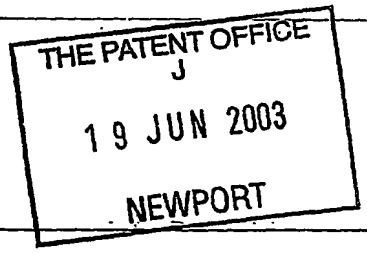

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1. Your reference

PAC 19.1

2. Patent application number
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— 0314246.0

~~19 JUN 2003~~

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CELLTECH R+D LIMITED,
208, BATH ROAD,
SLOUGH,
SL1 3WE

Patents ADP number *(if you know it)* —

If the applicant is a corporate body, give the country/state of its incorporation

UK

8121485001

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

—

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

FAO:- H. KENDALL,
CELLTECH R+D LTD,
ABINGTON,
CAMBRIDGE,
CB1 6GS

Patents ADP number *(if you know it)* —

8104198001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
—	—	—

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
—	—

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Description	32
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Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this applic

FOR AND ON BEHALF OF CELLTECH R&D LTD

Signature	Date
N.J. Kendall	18th June 2003

12. Name and daytime telephone number of person to contact in the United Kingdom — H. KENDALL — 01223 896499

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CHEMICAL COMPOUNDS

Field of the Invention

This invention relates to a series of novel hydroxamate sulfonamides and their derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Background of the Invention

CD23, which is also known as the low affinity receptor for immunoglobulin (Ig)E (FcεRII) is a type II integral protein expressed on a variety of haematopoietic and structural cells. In humans CD23 is a Ca^{2+} dependant C-type lectin of 45kDa and exists under two forms, CD23a and CD23b (Clin. And Exp. Allergy, 2000, 30, pp. 602-605). Both types are found on B-cells, CD23a is expressed constitutively and CD23b is induced in particular by IL-4. The b isoform is also found on non-B cells such as T-cells, Langerhans cells, monocytes, macrophages, platelets and eosinophils.

CD23 is not only an IgE receptor, but also a membrane-bound precursor of soluble molecules that still bind IgE (sCD23 or IgE-binding factors) (Sarfati. M. *et al*, Immunol. Res., 1992, 11, pp. 260-272). sCD23 of molecular weights 37, 33, 29, 25 and 17kDa arise by an autocatalytic cleavage process involving a metalloprotease cleavage of membrane-bound CD23 (Marolewski, A *et al*, Biochem. J., 1998, 333, pp. 573-579).

Membrane bound CD23 is a multifunctional molecule, which may exert different functions according to the cell type on which it is expressed, ranging from cellular adhesion, antigen presentation, growth and differentiation of B and T cells, rescue from apoptosis, release of cytotoxic mediators and regulation of IgE synthesis (Bonnefoy J. *et al*, Int. Rev. Immunol., 1997, 16, pp. 113-128). It has been postulated that CD23 is overexpressed in several pathologic conditions such as allergic, autoimmune, parasite diseases and B-cell lymphoproliferative diseases, such as chronic lymphocytic leukemia.

There is increasing evidence that sCD23 fragments may exert several effects, either alone or in conjunction with other cytokines, on a large variety of

haematopoietic cells. These effects include the regulation of IgE synthesis, promotion of B- and T- cell proliferation, inhibition of monocyte migration and in synergy with interleukin 1 (IL1) it may be implicated in the differentiation of early thymoctes, myeloid cell precursors and some germinal centre B cells.

In particular the three higher molecular weight sCD23 fragments (37, 33 and 29 kDa) have multifunctional cytokine properties which appear to play a major role in IgE production. The excessive formation of sCD23 has been implicated in the overproduction of IgE, which is the hallmark of allergic diseases such as extrinsic asthma, rhinitis, allergic conjunctivitis, eczema, atopic dermatitis and anaphylaxis (Sutton and Gould, Nature, 1993, 366, pp421-428). Elevated levels of sCD23 have also been observed in the synovial fluids of patients with rheumatoid arthritis (Chomarat P *et al*, Arthritis and Rheumatism, 1993, 36, pp. 234-242).

It has been shown that crosslinking CD23 at the cell surface by IgE delivers a negative feedback for IgE production and inhibits the release of sCD23. However, sCD23 fragments larger than 25kDa that retain part of the stalk region may promote IgE production by at least two mechanisms: 1) sCD23 directly stimulates IgE production possibly through CD21 triggering; 2) sCD23 fragments are capable of trapping IgE in the medium and thus may prevent negative feedback through membrane-bound CD23. Thus, compounds which have the ability to inhibit the formation of sCD23 should have twofold actions of: 1) inhibiting the immunostimulatory activities of the higher molecular weight soluble fragments; 2) enhancing negative feedback inhibition of IgE synthesis by maintaining levels of CD23 on the surface of B-cells. In addition, inhibition of CD23 cleavage should lessen sCD23-induced monocyte activation and mediator formation, therby reducing the inflammatory response

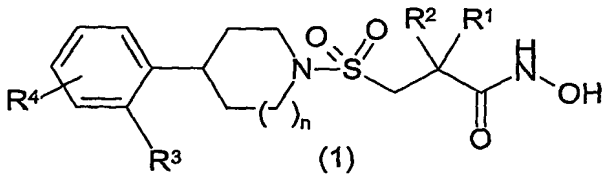
Until recently the therapeutic approach to modulating allergic responses has been focussed on the mediators thought to cause the response rather than addressing directly the control of IgE production (Christie G. *et al*, Eur. J. Immunol. 1997, 27, pp. 3228-3235). One proposed approach for a

therapeutically relevant control point in the regulation of IgE synthesis is the regulation of CD23 processing to sCD23.

Summary of the Invention

We have now found a class of hydroxamate sulfonamides which are potent inhibitors of CD23 shedding. Therefore the compounds are particularly suitable for the treatment and / or prophylaxis of allergic diseases associated with IgE production.

Thus we provide a compound of formula (1):



(1)

wherein:

n is zero or the integer 1;

R^1 is a group selected from C_{1-6}alkyl, aryl, heteroaryl, heterocycloalkyl, C_{3-6}cycloalkyl, -C_{1-6}alkylaryl, -C_{1-6}alkylheteroaryl, -C_{1-6}alkylheterocycloalkyl or -C_{1-6}alkylC_{3-6}cycloalkyl, in which each aryl or heteroaryl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^7, wherein each R^7 may be the same or different, and is an atom or group selected from F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy or –CN; and in which each alkyl, heterocycloalkyl and cycloalkyl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^8, wherein each R^8 may be the same or different, and is an atom or group selected from F, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, =O or =NOR^{10};

R^{10} is a hydrogen atom or a C_{1-3}alkyl group;

R^2 is a hydrogen atom;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl group optionally substituted with 1, 2 or 3 substituents selected from the group R^9, wherein each R^9 may be the same or different, and is an atom or group selected from F, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, =O or =NOR^{10};

R^3 is an atom or group selected from F, Cl, Br, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkoxy, C_{1-3}haloalkoxy or –CN;

R^4 is a hydrogen, F, Cl or Br atom or a C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkoxy, C_{1-3}haloalkoxy, -CN, $-SO_2R^5$, $-SO_2N(R^6)_2$, $-CON(R^6)_2$, $-N(R^6)_2$, $-NSO_2R^5$ or $-NCOR^5$ group, in which each R^6 group may be the same or different;

R^5 is a C_{1-3}alkyl group;

R^6 is a hydrogen atom or a C_{1-3}alkyl group;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

Description of the Invention

It will be appreciated that certain compounds of formula (1) may exist as geometric isomers (E or Z isomers). The compounds may also have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is to be understood to extend to all such geometric isomers, enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (1) may exist as tautomers, for example keto ($CH_2C=O$) – enol ($CH=CHOH$) tautomers.

It will also be appreciated that where desired the compounds of the invention may be administered in a pharmaceutically acceptable pro-drug form, for example, as a protected hydroxamic acid derivative, e.g. as either N or O substituted derivatives, such as O-benzoyl. It will be further appreciated that the pro-drugs may be converted *in vivo* to the active compounds of formula (1), and the invention is intended to extend to such pro-drugs.

In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

Thus as used herein the term "C_{1-6}alkyl", whether present as a group or part of a group, refers to straight or branched C_{1-6}alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl or neopentyl. The term "C_{1-}

$_3$alkyl" refers to a straight or branched C_{1-3}alkyl group selected from methyl, ethyl, n-propyl or i-propyl.

The term "C_{3-6}cycloalkyl group" refers to non-aromatic cyclic, saturated C_{3-6} ring systems selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "heterocycloalkyl group" refers to a 3 to 10 membered saturated monocyclic or multicyclic hydrocarbon ring system containing one, two, or three L^2 linker atoms or groups. Particular examples of suitable L^2 atoms or groups include -O- or -S- or -N(R^{11})-, where R^{11} is a hydrogen atom or a C_{1-6} alkyl group.

Particular examples of heterocycloalkyl groups include 3-7 membered monocyclic ring systems such as azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl pyrroldinyl, oxazolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, piperidinyl, 1,4 dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, N-C_{1-6} alkylpiperazinyl, N-C_{1-6}alkylpyrrolidinyl, N-C_{1-6}alkylpiperidinyl, N-C_{1-6} alkylmorpholinyl, homopiperazinyl or 7-10 membered multicyclic ring systems such as quinuclidinyl or 1,4-dioxaspiro[4.5]decane.

Heterocycloalkyl groups may be linked to the remainder of the compound of formula (1) by any available carbon atom or, when part of the group -C_{1-6}alkylheterocycloalkyl, by any carbon or hetero e.g. nitrogen atom as appropriate.

The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

The term "C_{1-6}haloalkyl" is intended to include the C_{1-6}alkyl groups as defined herein substituted by one, two or three of the halogen atoms just described. Similarly the term "C_{1-3}haloalkyl" is intended to include the C_{1-3}alkyl groups as defined herein substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include -CF_3, -CCl_3, -CHF_2, -$CHCl_2$, -CH_2F or -CH_2Cl groups.

The term "C_{1-6}alkoxy" as used herein refers to straight or branched C_{1-6}alkoxy groups such as methoxy, ethoxy, n-propoxy, i-propoxy or t-butoxy. Likewise the term "C_{1-3}alkoxy" as used herein refers to straight or branched C_{1-3}alkoxy groups such as methoxy, ethoxy, n-propoxy or i-propoxy.

The term "C_{1-6}haloalkoxy" as used herein includes any of those C_{16}alkoxy groups substituted by one, two or three halogen atoms as described above. Similarly the term "C_{1-3}haloalkoxy" includes any of those C_{1-3}alkoxy groups as defined herein substituted by one, two or three halogen atoms as described above. Particular examples include $-OCF_3$, $-OCCl_3$, $-OCHF_2$, $-OCHCl_2$, $-OCH_2F$ or $-OCH_2Cl$ groups.

The term "aryl" refers to an aromatic carbocyclic radical having a single ring or two condensed rings. This term includes, for example, phenyl or naphthyl.

The term "heteroaryl" refers to a 5 to 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one, two or three atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulfur (or oxidised versions thereof, such as N-oxide). Monocyclic heteroaryl groups include, for example, five or six membered heteroaryl groups containing one, two or three heteroatoms selected from oxygen, sulfur or nitrogen atoms.

Particular examples of monocyclic ring heteroaryl groups of this type include pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, tetrazolyl, triazinyl or pyridyl-N-oxide.

Particular examples of bicyclic ring heteroaryl groups of this type include benzofuryl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl or isoquinolinyl.

The heteroaryl groups may be attached to the remainder of the compound of formula (1) by any available carbon atom.

The terms "-C_{1-6}alkylaryl", "-C_{1-6}alkylheteroaryl", "-C_{1-6} alkylheterocycloalkyl" and "-C_{1-6}alkylC_{3-6}cycloalkyl" refer to a C_{1-6}alkyl group as defined herein in which a terminal hydrogen atom herein is replaced by an aryl, heteroaryl, heterocycloalkyl or C_{3-6}cycloalkyl group as described herein.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include

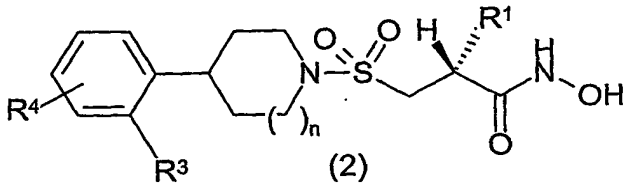
pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

One group of compounds of formula (1) has the formula (2):

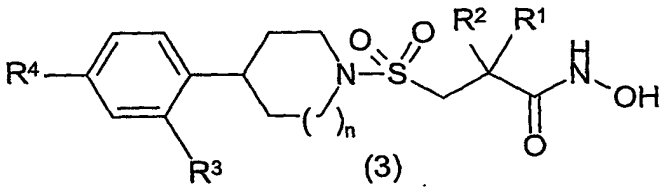


(2)

wherein n, R^1, R^3 and R^4 are as defined herein for compounds of formula (1);

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

Another group of compounds of formula (1)has the formula (3):

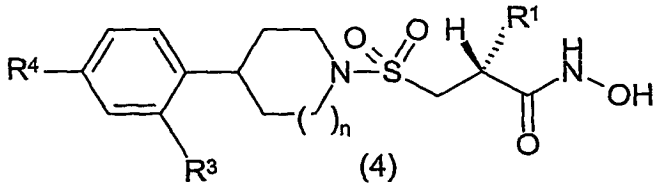


(3)

wherein n, R^1, R^2, R^3 and R^4 are as defined herein for compounds of formula (1);

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

One particular group of compounds of formula (3) has the formula (4):



(4)

wherein n, R^1, R^2, R^3 and R^4 are as defined herein;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

In one group of compounds of formulae (1), (2), (3) or (4) n is preferably the integer 1.

R^1, in one group of compounds of formulae (1), (2), (3) or (4) is a group selected from C_{1-6}alkyl, phenyl, heteroaryl, heterocycloalkyl, C_{3-6} cycloalkyl, -$(CH_2)_{1-2}$phenyl, -$(CH_2)_{1-2}$heteroaryl, -$(CH_2)_{1-2}$heterocycloalkyl or -$(CH_2)_{1-2}C_{3-6}$cycloalkyl, in which each phenyl or heteroaryl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^7, as herein defined; and in which each alkyl, heterocycloalkyl and cycloalkyl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^8, as herein defined. R^1 in a further group of compounds of formulae (1), (2), (3) or (4) is a group selected from optionally substituted C_{1-6}alkyl, phenyl, heterocycloalkyl, C_{3-6}cycloalkyl or -$(CH_2)_{1-2}$phenyl.

Particular R^1 examples of this type include optionally substituted C_{1-6}alkyl, e.g. i-propyl, phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, imidazolyl, N-C_{1-6}alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, 1,4-dioxaspiro[4.5]decane, cyclobutyl, cyclopentyl, cyclohexyl, –CH_2phenyl or –CH_2pyridyl.

R^7, in compounds of the invention, may be for example an atom or group selected from F, Cl, methyl, -CF_3, -CF_2H, methoxy, -OCF_3, -OCF_2H or –CN.

R^8, in compounds of the invention, may be for example an atom or group selected from F, methyl, -CF_3, -CF_2H, methoxy, -OCF_3, -OCF_2H, =O, =NOH or =$NOCH_3$.

R^1, in one particular group of compounds of formulae(1), (2), (3) or (4), is an i-propyl, phenyl, 3,4-difluorophenyl, tetrahydropyranyl, cyclopentyl,–CH_2phenyl or –(CH_2)3,4-difluorophenyl group especially i-propyl, phenyl or –CH_2phenyl.

Another group of compounds of the invention has the formulae (1) or (3) wherein R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl group, particularly cyclobutyl, optionally substituted with R^9 as defined herein.

R^9, in one group of compounds of the invention, is an atom or group selected from F, methyl, -CF_3, -CF_2H, methoxy, -OCF_3, -OCF_2H, =O, =NOH or =$NOCH_3$.

Particular R^3 examples include F, Cl, methyl, ethyl, i-propyl, -CF_3, -CF_2H, methoxy, ethoxy, -OCF_3, -OCF_2H or –CN. R^3, in one group of compounds of formulae (1), (2), (3) or (4), is a F atom or a methyl, -CF_3, methoxy or –OCF_2H group.

Particular R^4 examples include hydrogen, F, Cl, methyl, ethyl, i-propyl, -CF_3, -CF_2H, methoxy, ethoxy, -OCF_3, -OCF_2H, –CN, -SO_2CH_3, -$SO_2N(H)_2$, -$SO_2N(CH_3)_2$, -$SO_2N(H)CH_3$, -$CON(H)_2$, -$CON(CH_3)_2$, -$CON(H)CH_3$, -$N(H)_2$, -$N(CH_3)_2$, -$N(H)CH_3$, -NSO_2CH_3 or -$NCOCH_3$. R^4, in one group of compounds of formulae (1), (2), (3) or (4), is a hydrogen, F or Cl atom or a methyl, -CF_3, methoxy or –OCF_2H group, especially a hydrogen, fluorine or chlorine atom.

Certain compounds of the invention also have a surprisingly good selectivity for CD23 when compared with their ability to inhibit matrix metalloproteinases. Examples of such matrix metalloproteinases include MMP 9 or MMP 13. Such compounds are particularly useful for the treatment of diseases in which CD23 has a role, for example allergic and other diseases as described herein. Compounds of the invention which have this useful property include those of formulae (1), (2), (3) or (4), wherein R^3 is an atom or group selected from F, Cl, C_{1-3}alkyl or C_{1-3}alkoxy. An especially preferred group of compounds is where R^3 is a C_{1-3}alkyl, particularly methyl, or C_{1-3}alkoxy, particularly methoxy group.

Particular compounds of this type include:

2-[4-(2-methoxyphenyl)piperidine-1-sulfonylmethyl]N-Hydroxy-3-methylbutyramide;

2-[4-(2-methyl-4-fluorophenyl)-piperidine-1-sulfonylmethyl]N-Hydroxy-3-methylbutyramide;

2-benzyl-N-Hydroxy-3-[4-(2-methoxyphenyl)-piperidine-1-sulfonyl] propionamide;

2-benzyl-N-Hydroxy-3-[4-(2-methylphenyl)-piperidine-1-sulfonyl] propionamide;

N-hydroxy-3-(4-(2-Methoxyphenyl)-piperidine-1-sulfonyl]-2-phenyl propionamide;

2(*R*)-[4-(2-methoxyphenyl)-piperidine-1-sulfonylmethyl]N-Hydroxy-3-methylbutyramide;

2(*R*)-[4-(2-methylphenyl)piperidine-1-sulfonylmethyl]N-Hydroxy-3-methylbutyramide;

1-[4-(2-methoxyphenyl)-piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide;

1-[4-(2-methylphenyl)piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

Compounds of formulae (1), (2), (3) or (4) are potent inhibitors of CD23 shedding. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter. The selectivity profile for certain compounds of the invention with respect to their inhibition of matrix metalloproteinases may be determined using the assay as described in Example D in the International Patent Application WO-A-98/05635.

Thus the compounds of the invention may be used in the treatment of conditions associated with increased levels of sCD23. The invention extends to such a use and in general to the use of the compounds of formulae(1), (2), (3) or (4) for the manufacture of a medicament for treating such diseases and disorders.

Particular uses to which the compounds of the invention may be put include allergic diseases such as asthma, atopic dermatitis and other atopic diseases, allergic rhinitis, gastrointestinal allergies such as food allergies, eosinophilia, conjunctivitis, glomerular nephritis, graft-v-host disease, systemic anaphylaxis or hypersensitivity responses, urticaria, shock, drug allergies, insect sting allergies or parasite infections.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of asthma, atopic dermatitis or allergic rhinitis .

Compounds of the invention may also be of use in other diseases where sCD23 is implicated including inflammatory diseases, such as, rheumatoid arthritis and psoriasis or neoplastic diseases, such as, lymphoma orleukemia.

The compounds of formulae (1), (2), (3) or (4) can be used alone or in combination with other compounds having related utilities to prevent and treat allergic disorders and diseases, including asthma and atopic dermatitis, as well as those pathologies as discussed herein.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formulae (1), (2), (3) or (4) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Alternate compositions of this invention comprise a compound of formulae (1), (2), (3) or (4) or a salt thereof; an additional agent selected from an immunosuppressant or an anti-inflammatory agent; and any pharmaceutically acceptable carrier, adjuvant or vehicle.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, vaginal or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional

means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formulae (1), (2), (3) or (4) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. For particle mediated administration the compounds offormulae (1), (2), (3) or (4) may be coated on particles such as microscopic gold particles.

In addition to the formulations described above, the compounds of formulae (1), (2), (3) or (4) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

For vaginal or rectal administration the compounds offormulae (1), (2), (3) or (4) may be formulated as a suppository. These formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is a solid at room temperature but liquid at the body temperature. Such materials include for example cocoa butter and polyethylene glycols.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

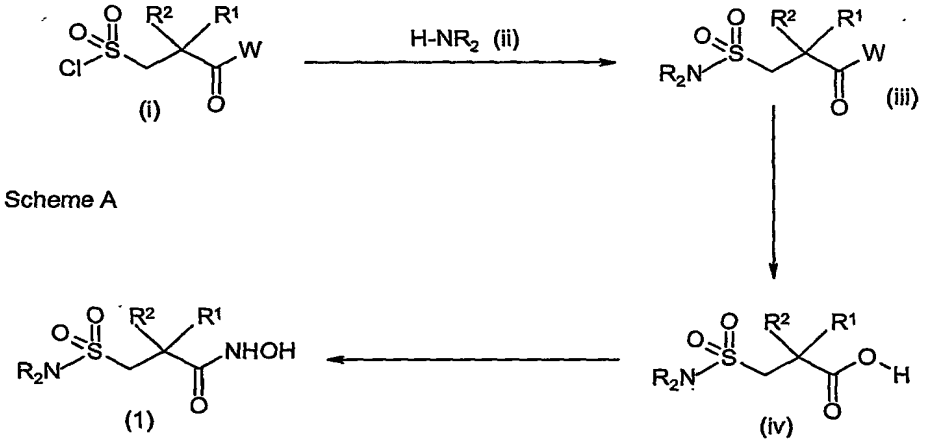
The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. Many of the reactions described are well-known standard synthetic methods which may be applied to a variety of compounds and as such can be used not only to generate compounds of the invention, but also where necessary the intermediates thereto.

In the following process description, the symbols n, R^1, R^2, R^3, R^4 when used in the formulae depicted are to be understood to represent those groups

described above in relation to formulae (1), (2), (3) or (4) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, (1999) and the examples herein]. In some instances, deprotection may be the final step in the synthesis of a compound of formulae (1), (2), (3) or (4) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to a further aspect of the invention, a compound of formula (1), or particular isomers thereof, may be prepared using the general methods a shown in Scheme A:



Scheme A

Thus, compounds of formula (iii), where W is for example an alkoxy group, such as methoxy, ethoxy or *tert*-butoxy or a chiral auxillary, for example, 4-(R)-benzyl-oxazolidin-2-one maybe prepared by methods well known in the literature, for example, by reaction of a sulfonyl chloride (i) with an amine (ii) in the presence of

an amine base, such as triethylamine in a halogenated solvent, such as dichloromethane at room temperature.

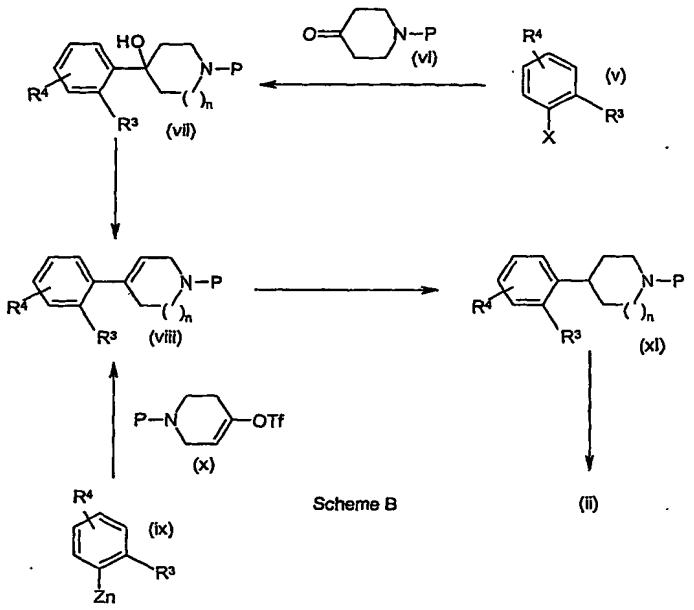
Compounds of general formula (i) are either known or may be made by one skilled in the art using conditions known in the literature, see for example WO-A-99/24399, or as described in the examples hereinafter. Compounds of general formula (ii) are available commercially or they be made using methods known in the literature or by any method known to those skilled in the art.

Carboxylic acids of general formula (iv) may be prepared by deprotection of a suitably protected carboxylic acid of formula (iii). For example, where W is an alkoxy group, such as ethoxy, a base such as aqueous lithium hydroxide may be used, alternatively trifluoroacetic acid may be used when W is a *tert*-butyl group or in the case of a chiral auxiliary such as 4-(R)-benzyl-oxazolidin-2-one, lithium hydroxide/hydrogen peroxide may be used. Appropriate solvent and temperature conditions such as those described in the examples herein after may be used.

Hydroxamic acids of general formula (1) may be prepared using conditions well known in the literature. For example, treatment of acids of formula (iv) with oxalyl chloride in an inert solvent (such as dichloromethane) gives an intermediate acid chloride, which may or may not be isolated, but which in turn is reacted with hydroxylamine at a suitable temperature such as room temperature to give the desired hydroxamic acids (1). Alternatively an acid of formula (iv) maybe activated *in situ* using for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, advantageously in the presence of a catalyst such as a N-hydroxy compound, e.g. N-hydroxybenzotriazole using suitable conditions, e.g. in *N,N* dimethylformamide at –15°C, prior to the subsequent addition of a suitably protected hydroxylamine such as *tert*-butyldimethyl silyl hydroxylamine and warming to ambient temperature. The protecting group maybe removed using appropriate conditions, such as water or tetrabutylammonium fluoride and acetic acid in tetrahydrofuran at 0°C, to yield the desired hydroxamic acids of formula (1).

Intermediates of formulae (i)-(iv) and any other intermediates required to obtain compounds of formulae (1), (2), (3) or (4), when not available commercially, may be prepared by methods known to those skilled in the art following procedures set forth in references such as *Rodd's Chemistry of Carbon Compounds*, Volumes 1-15 and Supplementals (Elsevier Science Publishers, 1989), *Fieser and Fieser's Reagents for Organic Synthesis*, Volumes 1-19 (John Wiley and Sons, 1999), *Comprehensive Heterocyclic Chemistry*, Ed. Katritzky *et al*, Volumes 1-8, 1984 and Volumes 1-11, 1994 (Pergamon), *Comprehensive Organic Functional Group Transformations*, Ed. Katritzky *et al*, Volumes 1-7, 1995 (Pergamon), *Comprehensive Organic Synthesis*, Ed. Trost and Flemming, Volumes 1-9, (Pergamon, 1991), *Encyclopedia of Reagents for Organic Synthesis* Ed. Paquette, Volumes 1-8 (John Wiley and Sons, 1995), *Larock's* Comprehensive Organic Transformations (VCH Publishers Inc., 1989) and *March's* Advanced Organic Chemistry (John Wiley and Sons, 1992).

Thus, for examples, an amine of general formula (ii) may be prepared using methods known to those skilled in the art, including the general methods as shown in Scheme B:



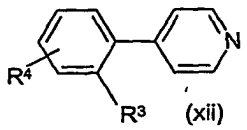
Scheme B

Where appropriate, aromatic halogen substituents (X e.g. = Br) in the compounds of general formula (v) may be subjected to halogen - metal exchange

by treatment with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with a ketone of general formula (vi) (where P is a suitable protecting group, such as carbobenzyloxy) to give an alcohol of formula (vii). The alcohol thus formed may then be dehydrated using standard conditions, such as acid catalysis, to yield a compound of formula (viii).

Alternatively a compound of formula (viii) may also be prepared by reaction of an aryl-zinc species of formula (ix) with a triflate of formula (x) in the presence of a catalyst, such as palladium, using conditions known to those skilled in the art. The compound of formula (viii) may then be reduced using standard methodology, such as palladium catalysed hydrogenation, to yield a compound of formula (xi), containing a protecting group, P which may be converted to a compound of formula (ii) using standard deprotection methods. It will be appreciated by those skilled in the art that different protecting groups (P) may be required at each stage of the synthesis in order to satisfy the reaction conditions and as such they may be interconverted using standard methods.

A compound of formula (ii) may also be prepared from a compound of formula (xii):



(xii)

by selective hydrogenation of the pyridine ring, for example using a palladium or nickel catalyst uder a hydrogen atomosphere. The compound of general formula (xii) may be prepared using methods known to those skilled in the art, such as standard biaryl coupling methodology.

It will be appreciated that compounds of formulae(1), (2), (3) or (4) or any preceding intermediates may be further derivatised by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these

methods may also be used to obtain or modify other compounds of any of formula (1), (2), (3) or (4) or any preceding intermediates where appropriate functional groups exist in these compounds.

Salts of compounds of formulae (1), (2), (3) or (4) may be prepared by reaction of a compound of formulae (1), (2), (3) or (4) with an appropriate base or acid in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol or an aqueous solvent using conventional procedures. Salts of compounds of formulae(1), (2), (3) or (4) may be exchanged for other salts by use of conventional ion-exchange chromatography procedures.

Where it is desired to obtain a particular enantiomer of a compound of formulae (1), (2), (3) or (4) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formulae (1), (2), (3) or (4) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

In another resolution process a racemate of formulae (1), (2), (3) or (4) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

The following Examples illustrate the invention All temperatures are in °C. Where experimental detail is not given for the preparation of a reagent it is either commercially available, or it is known in the literature, for which the CAS number is quoted. The compounds are named with the aid of Beilstein Autonom supplied

by MDL Information Systems GmbH, Theodor-Heuss-Allee 108, D-60486 Frankfurt, Germany.

^{1}H NMR spectra were obtained at 300MHz or 400MHz unless otherwise indicated.

The following LCMS conditions were used to obtained the retention times (RT) as described herein:

LCMS conditions:

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionization

Column: Luna C18(2) 100x4.6mm, 5µm particle size Analytical column
Column Temp: 35°C
Mobile Phase: A: Water + 0.08% formic acid
B: Acetonitrile + 0.1% formic acid
Flow rate: 3ml/min
Gradient:

Time (mins):	% Composition B:
0	5
4.4	95
5.30	95
5.32	5
6.5	5
6.6	

Run time: 6.5 mins
Typical Injection Vol: 5µl
Detector Wavelength: DAD 205-330nm

Preparative LC conditions:

Gilson 215 liquid handler setup.

Column: Luna C18(2) 250x21.2mm, 5µn particle size PREP column
Column Temp: Ambient
Mobile Phase: A: Water + 0.08% formic acid
B: Acetonitrile + 0.1% formic acid
Gradient: Variable – depends on retention of sample in LCMS screen
Run Time: 20 mins
Flow rate: 20ml/min
Typical Injection Vol: 750µl of 25mg/ml solution
Detector Wavelength: 210 and 254nm

Abbreviations used:

DCM – Dichloromethane
THF – Tetrahydrofuran
MeOH – Methanol
DMF – N,N-dimethylformamide
TFA- Trifluoroacetic acid
MTBE – *tert*-butyl methyl ether

nBuLi – n-butyllithium Hunig's base – N,N-diisopropylethylamine

$CDCl_3$ – Deuterated chloroform d_6DMSO – Deuterated dimethylsulfoxide

Methanol-d_4 – Deuterated methanol

Intermediate 1

3-Methyl-2-methylenebutyric acid

Isopropyl malonic acid (30 g) was dissolved in dioxan (200 ml) and piperidine (30 ml) was added, followed by aqueous formaldehyde (30 ml). The solution was stirred overnight and the resulting thick white suspension was heated to 100°C for 2 h, then cooled and evaporated. The mixture was diluted with water (400 ml) and washed with ether (200 ml), then acidified with citric acid to pH 4 and extracted with DCM (200 ml). The solvent was washed with water (200 ml) and brine (200 ml), dried and evaporated to give the title compound as colourless solid 25 g. MS 114 (M)

Intermediate 2

2-Bromomethyl-3-methylbutyric acid

3-Methyl-2-methylenebutyric acid (25 g) was dissolved in 48% hydrobromic acid in acetic acid (100 ml) and the solution stirred overnight at room temperature, then added to water (300 ml) and extracted with diethyl ether (2 x 200 ml). The solvent washed with water (200 ml) and brine (200 ml), dried and evaporated to give the title compound as a pale amber solid 33 g. MS 195 (M)

Intermediate 3

2-Bromomethyl-3-methylbutyric acid *tert*-butyl ester

2-Bromomethyl-3-methylbutyric acid (33 g) was placed in a Parr pressure reactor, cooled to –78 °C and isobutylene (200 ml) and DCM (200 ml) were added, followed by concentrated sulphuric acid (1 ml). The vessel was sealed and the mixture stirred at room temperature for 18 h, then pressure carefully released and the solution added to saturated sodium bicarbonate solution (400 ml). The mixture was extracted with diethyl ether (2 x 200 ml), the solvent washed with water (200 ml) and brine (200 ml) and evaporated *in vacuo* to give the title compound as a colourless liquid (33 g). MS 251 (M)

Intermediate 4

2-Acetylsulfanylmethyl-3-methylbutyric acid *tert*-butyl ester

Potassium thioacetate (20 g) was added to a solution of 2-bromomethyl-3-methylbutyric acid *tert*-butyl ester (33 g) in DMF (200 ml) and the brown mixture stirred for 18 h, then added to water (1 litre), and the mixture extracted with diethyl ether (300 ml). The solvent was washed with water, saturated sodium bicarbonate solution and brine, dried and evaporated to give the title compound as an amber oil (29 g). MS 246 (M)

Intermediate 5

2-Chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester

Chlorine was passed through a solution of 2-acetylsulfanylmethyl-3-methylbutyric acid *tert*-butyl ester (29 g) in DCM (100 ml) and water (100 ml) at 0°C for 1 h, giving a pale green solution. The phases were separated and the organic layer washed with water (200 ml), sodium bicarbonate solution (200 ml) and brine (200 ml), dried and evaporated to give the product as a colourless liquid which crystallised on refrigeration (27 g). MS 271 (M)

Intermediate 6

2-Benzyl acrylic acid

Prepared from benzyl malonic acid (25g) using the method as described for 3 methyl-2-methylenebutyric acid to give the title compound as white solid (18 g). MS 162 (M + 1)

Intermediate 7

2-Bromomethyl-3-phenylpropionic acid

Prepared from 2-benzyl acrylic acid (18 g) using the method as described for 2 bromomethyl-3-methylbutyric acid to give the title compound as a white solid (23 g). MS 243 (M)

Intermediate 8

2-Bromomethyl-3-phenylpropionic acid- *tert*-butyl ester

Prepared using the method as described for 2-bromomethyl-3-methylbutyric acid *tert*-butyl ester from 2-bromomethyl-3-phenylpropionic acid (23 g) to give the title compound as a brown oil 28 g. MS 299 (M)

Intermediate 9

2-Acetylsulfanylmethyl-3-phenylpropionic acid- *tert*-butyl ester

Prepared using the method as described for 2-acetylsulfanylmethyl-3-methylbutyric acid *tert*-butyl ester from 2-bromomethyl-3-phenylpropionic acid-*tert*-butyl ester (28 g) to give the title compound as a yellow oil (18.5 g). MS 294 (M)

Intermediate 10

2-(Chlorosulfonylmethyl)-3-phenylpropionic acid- *tert*-butyl ester

Prepared using the method as described for 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester from 2-acetylsulfanylmethyl-3-phenylpropionic acid-*tert*-butyl ester (18.5 g) as a colourless solid (19 g). MS 319 (M + H).

Intermediate 11

1-(Chlorosulfonylmethyl)cyclobutane carboxylic acid ethyl ester

N-Butyl lithium (49.8 ml of 1.6M solution in hexanes) was added to a solution of di-isopropylamine (11.2 ml) in THF (90 ml) at –78 °C and the solution stirred for 30 min. A solution of ethyl cyclobutane carboxylate (10 ml) was added dropwise and the mixture stirred for 30 min, then treated with diiodomethane (6.4 ml). The mixture was stirred for 3 h and allowed to warm to room temperature, quenched with water (50 ml) and evaporated. The residual mixture was partitioned between water and ethyl acetate, the organic layer washed with water and brined, dried and evaporated. The residue was dissolved in DMF (50 ml) and potassium thioacetate (8.3 g) was added. The brown solution was stirred overnight at room temperature, then added to water and extracted with ethyl acetate. The solvent was washed with water (200 ml) and brine (200 ml), dried and evaporated to a brown oil. The residue was dissolved in DCM (100 ml), water (100 ml) was added and chlorine bubbled through the mixture at 0°C. The organic layer was washed with water (200 ml) and brine (200 ml), dried and evaporated to give the title compound as a brown oil (9.8 g).

TLC R_f 0.45 (2:1 heptane-ethyl acetate).

Intermediate 12

4-(R)-Benzyl-3-(3-methylbutyryl)oxazolidin-2-one

nButyllithium (2.5 M in hexanes, 65 ml) was added to a solution of (*R*)-benzyloxazolidinone (28.9 g) in THF (200 ml) at – 78°C and the mixture was stirred for 30 min, then 3-methylbutanoyl chloride (22 ml) was added and the solution stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride, evaporated *in vacuo* and the residue extracted with DCM (2 x 200 ml). The solvent was washed with water (200 ml), bicarbonate solution (200 ml) and brine (200 ml), dried and evaporated to give the title compound as a colourless solid (41.5 g). MS 261 (M)

Intermediate 13

4-(R)-Benzyl-3-(2-(S)-hydroxymethyl-3-methylbutyryl) oxazolidin-2-one

Titanium tetrachloride (18 ml) was added to a solution 4-(R)-benzyl-3-(3-methylbutyryl)oxazolidin-2-one (41.5 g) in DCM at 0 °C. Hunig's base (28 ml) was added and the purple solution stirred for 30 min, then a solution of trioxane (11.2 g) in DCM was added dropwise, followed by titanium tetrachloride. The mixture was stirred vigorously for 2 h at 0°C, giving an amber solution, which was quenched with saturated aqueous ammonium chloride. The phases were separated and the organic layer washed with water (150 ml), bicarbonate solution (150 ml), and brine(150 ml), dried and evaporated to a white solid (45 g).
MS 291 (M).

Intermediate 14

4-(R)-Benzyl-3-(2-(R)-iodomethyl-3-methylbutyryl)oxazolidin-2-one

Iodine (42 g), triphenylphosphine (47 g) and imidazole (12 g) were added to a solution of 4-(R)-benzyl-3-(2-(S)-hydroxymethyl-3-methylbutyryl) oxazolidin-2-one (45 g) in toluene (500 ml) and the mixture was boiled under reflux for 1 h. The resulting suspension was cooled, filtered and the filtrate washed with water (150 ml), and brine (150 ml),. The solid residue was dissolved in DCM and filtered through silica (200 g) eluting with ether/hexane to give the title compound as a pale yellow oil (57 g). MS 401 (M)

Intermediate 15

4-(R)-Benzyl-3-(2-(R)-acetylthiomethyl-3-methylbutyryl) oxazolidin-2-one

Potassium thioacetate (19 g) was added to a solution of 4-(R)-benzyl-3-(2-iodomethyl-3-methylbutyryl)oxazolidin-2-one (56 g) in DMF (300 ml) and the mixture was stirred at room temperature for 3 h, then added to water (2 l) and extracted with ether (2 x 500 ml). The solvent was washed with water (400 ml), bicarbonate solution (200 ml) and brine (200 ml), dried and evaporated to give the title compound as a pale amber oil (49 g). MS 349 (M)

Intermediate 16

4(R)-Benzyl-3-(2(R)-chlorosulfonylmethyl-3-methylbutyryl)oxazolidin-2-one

Chlorine was bubbled through a solution of 4-(R)-benzyl-3-(2-(R)-acetylthiomethyl-3-methylbutyryl) oxazolidin-2-one (49g) in DCM (200 ml) and water (200 ml) until the solution became yellow. The mixture was stirred vigorously for 1 h, then purged with nitrogen, the phases were separated and the organic layer washed with water (150 ml), and brine (150 ml), dried and evaporated to give the title compound as a colourless gum (42 g). MS 373 (M)

1H NMR (δH, CDCl3) 7.2-7.4 (5H, m), 4.65-4.8 (2H, m), 4.45 (1H, dd), 4.20 (2H, d), 3.70 (1H, dd), 3.45 (1H, dd), 2.65 (1H, dd), 2.10 (1H, m), 1.15 (3H, d), 0.03 (3H, d)

Intermediate 17

3-Bromo-2-phenylpropionic acid

Prepared from phenylmalonic acid [CAS number 492-38-6] (4 g) following the procedure as described for 2-bromomethyl-3-methylbutyric acid to yield an amber oil (5.2 g). MS 229 (M)

Intermediate 18

3-Bromo-2-phenylpropionic acid-*tert*-butyl ester

Prepared using the method as described for 2-bromomethyl-3-methylbutyric acid *tert*-butyl ester from 3-bromo-2-phenylpropionic acid (5g) as a colourless oil (4.5 g). MS 285 (M)

Intermediate 19

3-Acetylsulfanyl-2-phenylpropionic acid-*tert*-butyl ester

Prepared using the method as described for 2-acetylsulfanylmethyl-3-methylbutyric acid *tert*-butyl ester from *tert*-butyl-3-bromo-2-phenylpropanoate (4 g) as a yellow liquid (3.3 g). MS 280 (M)

Intermediate 20

3-Chlorosulfonyl-2-phenylpropionic acid-*tert*-butyl ester

Prepared using the method as described for 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester from 3-acetylsulfanyl-2-phenylpropionic acid-*tert*-butyl ester (3 g) as a beige solid (2.1 g). TLC R_f 0.47 (ether)

Method A

Example 1

2-[4-(2-Ethoxyphenyl)piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

2-Ethoxyphenylpiperidine [CAS 100617-80-9] (100 mg) was added to a solution of 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (120 mg) in DCM (10 ml) and triethylamine (50 mg). The solution was stirred for 18 h, then washed with citric acid solution, water and brine, the solvent dried and evaporated. The residue was redissolved in DCM (10 ml) and TFA (2 ml) added. The solution was stirred for 3 h, then evaporated and azeotroped to dryness, the residue dissolved in DCM (10 ML) and washed with water (20 ml) and brine (20 ml). Oxalyl chloride (200 mg) and DMF (1 drop) were added, the solution stirred for 3h, then evaporated to dryness. The residue was dissolved in THF (10 ml) and aqueous hydroxylamine (0.5 ml) added. The mixture was stirred for 2 h, diluted with water (10 ml) and evaporated to remove THF. The aqueous mixture was extracted with DCM (20 ml), the solvent washed with water (10 ml) and brine (7 ml), dried and evaporated and the residue recrystallised from ether-hexane to give the title compound as a white solid. MS 399 (M + H) 1H NMR (δH, $CDCl_3$) 8.9 (2H, br s), 7.2 (2H, m), 6.8-7.0 (2H, m), 4.1 (2H, q), 3.8 (2H, m), 3.5 (1H, dd), 2.8-3.1 (4H, m), 2.5 (1H, m), 1.7-2.1 (5H, m), 1.30 (3H, t), 1.0 (6H, appears as triplet)

Similarly prepared using method A were:

Example 2

2-[4-(2-Chlorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-chlorophenyl)piperidine [CAS 82211-92-5] (230 mg) and 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (270 mg) as a white solid (70 mg). MS 389 (M + H) 1H NMR (δH, $CDCl_3$) 8.5 (2H, br s), 7.1-7.4 (4H, m), 3.9 (2H, m), 3.5 (1H, dd), 3.2 (1H, m), 3.0 (1H, dd), 2.9 (2H, m), 2.4 (1H, m), 1.6-2.0 (5H, m), 1.0 (6H, appears as triplet)

Example 3

2-[4-(2-Methoxyphenyl)piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-methoxy-4-chlorophenyl)piperidine (70 mg) and 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (80 mg) as a white solid (30 mg). MS 419 (M + H). 1H NMR (δH, $CDCl_3$) 8.7 (2H, br s), 7.1 (1H, d), 6.85 (1H, d), 6.8 (1H, s), 3.85 (3H, s), 3.7-3.9 (2H, m), 3.5 (1H, dd), 3.0 (2H, m), 2.8-2.9 (2H, m), 2.4 (1H, m), 1.5-2.0 (5H, m), 1.0 (6H, appears as triplet)

Example 4

2-[4-(2-Methyl-4-fluorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-methyl-4-fluorophenyl)piperidine [CAS 27729596-2] (140 mg) and 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (160 mg) as a white solid (5.9 mg). MS 387 (M + H) 1H NMR (δH, d_6DMSO) 10.7 (1H, s), 9.0 (1H, s), 7.4 (1H, m), 7.1 (2H, m), 3.7-3.9 (2H, m), 3.6 (1H, dd), 3.1 (1H, dd), 2.8-3.1 (3H, m), 2.4 (3H, s) 2.3-2.4 (1H, m), 1.7-2.0 (5H, m), 1.0 (6H, appears as doublet)

Example 5

2-[4-(2-Difluoromethoxyphenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-difluoromethoxyphenyl)piperidine (200 mg) and 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (220 mg) as a white solid (120 mg). MS 421 (M + H). 1H NMR (δH, $CDCl_3$) 8.6 (2H, br s), 7.2-7.4

(3H, m), 7.1 (1H, d), 6.5 (1H, t), 3.9 (2H, m), 3.5 (1H, dd), 3.1 (1H, tt), 3.0 (1H, dd), 2.8-2.9 (2H, m), 2.4 (1H, dt), 2.0 (1H, m), 1.6-1.9 (4H, m), 1.0 (6H, appears as triplet).

Example 6

2-[4-(2-Fluorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 2-chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (270 mg) and 4-(2-fluorophenyl)piperidine (220 mg) as a white solid 130 mg. MS 273 (M + H). 1H NMR (δH, d_6DMSO) 10.6 (1H, s), 8.9 (1H, s), 7.0-7.4 (4H, m) 3.7-3.9 (2H, m), 3.6 (1H, dd), 3.2 (1H, dd), 2.8-3.1 (3H, m), 2.3 (1H, m), 1.8-2.1 (5H, m), 0.95 (6H, appears as doublet)

Example 7

2-[4-(2-Trifluorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-trifluoromethylphenyl)piperidine (270 mg) and 2 chlorosulfonylmethyl-3-methyl-butyric acid *tert*-butyl ester (270 mg) as a white solid (160 mg). MS 423 (M + H). 1 H NMR (δH, d_6DMSO) 10.8 (1H, s), 9.1 (1H, s), 7.2-7.6 (4H, m) 3.8-4.0 (2H, m), 3.7 (1H, dd), 3.1 (1H, dd), 3.1 (1H, m), 2.8-3.0 (2H, m), 2.4 (1H, m), 1.7-2.0 (5H, m), 1.0 (6H, appears as doublet)

Example 8

2-Benzyl-N-Hydroxy-3-[4-(2-trifluoromethylphenyl)-piperidine-1-sulfonyl]propionamide

Prepared from 2-(chlorosulfonylmethyl)-3-phenylpropionic acid-*tert*-butyl ester (160 mg) and 4-(2-trifluoromethylphenyl)piperidine (120 mg) as a white solid (8.4 mg) after purification by preparative HPLC. MS 471 (M + 1). 1H NMR (δH, $CDCl_3$) 8.6 (2H, s), 7.6 (1H, d), 7.4 (1H, t), 7.35 (1H, d), 7.1-7.4 (6H, m), 3.8 (2H, m), 3.6 (1H, dd), 2.6-3.1 (7H, m), 1.6-1.9 (4H, m)

Example 9

2-Benzyl-N-Hydroxy-3-[4-(2-fluorophenyl)-piperidine-1-sulfonyl] propionamide

Prepared from 2-(chlorosulfonylmethyl)-3-phenylpropionic acid-*tert*-butyl ester (150 mg) and 4-(2-fluorophenyl)piperidine (100 mg) as a white solid (14mg) after preparative HPLC. MS 421 (M + 1). 1H NMR (δH, $CDCl_3$) 8.6 (2H, s), 6.9-7.4 (9H, m), 3.8 (2H, m), 3.6 (1H, dd), 2.6-3.1 (7H, m), 1.6-1.9 (4H, m)

Example 10

2-Benzyl-N-Hydroxy-3-[4-(2-methoxyphenyl)-piperidine-1-sulfonyl] propionamide

From 2-(chlorosulfonylmethyl)-3-phenylpropionic acid-*tert*-butyl ester (150 mg) and 4-(2-methoxyphenyl)piperidine (100 mg) as a white solid (1.2 mg) after preparative HPLC. MS 433 (M + 1). 1H NMR (δH, $CDCl_3$) 8.5 (2H, br s), 7.2-7.5 (5H, m), 6.8-7.0 (4H, m), 3.8 (3H, s), 3.8 (2H, m), 3.6 (1H, dd), 2.6-3.1 (7H, m), 1.6-1.9 (4H, m)

Example 11

2-Benzyl-N-Hydroxy-3-[4-(2-methylphenyl)-piperidine-1-sulfonyl] propionamide

Prepared from 2-(chlorosulfonylmethyl)-3-phenylpropionic acid-*tert*-butyl ester (320 mg) and 4-(2-methylphenyl)piperidine (200 mg) as a white solid (150 mg). MS 417 (M + 1). 1H NMR (δH, $CDCl_3$) 8.5 (2H, br s), 7.2-7.5 (5H, m), 6.8-7.0 (4H, m), 3.8 (2H, m), 3.6 (1H, dd), 2.6-3.1 (7H, m), 2.4 (3H, s), 1.6-1.9 (4H, m)

Example 12

N-Hydroxy-3-(4-(2-Methoxyphenyl)-piperidine-1-sulfonyl]-2-phenyl propionamide

Prepared from 3-chlorosulfonyl-2-phenylpropionic acid-*tert*-butyl ester (230 mg) and 4-(2-methoxyphenyl)piperidine (160 mg) as a beige solid (35 mg). MS 419 (M + 1). 1H NMR (δH, d_6DMSO) 10.9 (1H, s), 8.9 (1H, s), 7.25-7.5 (5H, m), 7.2 (2H, m), 6.9 (1H, d), 6.85 (1H, t), 3.9 (1H, dd), 3.8 (1H, dd), 3.75 (3H, s), 3.6 (2H, m), 3.25 (1H, dd), 2.96 (1H, m), 2.7-2.9 (2H, m), 1.5-1.9 (4H, m)

Method B

Example 13

2(*R*)-[4-(2-Methoxyphenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

4-(2-Methoxyphenyl)piperidine (230 mg) was added to a solution of4(R)-benzyl-3-(2(R)-chlorosulfonylmethyl-3-methylbutyryl)oxazolidin-2-one (373 mg) in DCM (10 ml) and triethylamine (200 mg) and the solution was stirred for 2 h at room temperature. The mixture was washed with aqueous citric acid, bicarbonate solution and brine, dried and evaporated. The residue was chromatographed on silica (30% ethyl acetate-hexane) and the product dissolved in THF. Hydrogen peroxide (0.15 ml) was added, the mixture cooled in ice and a solution of lithium hydroxide (40 mg) in water (5 ml) was added dropwise. The mixture was stirred for 2h, quenched with aqueous sodium sulphite (10% wt/v, 20 ml), then evaporated to half volume *in vacuo*. The aqueous layer was washed with DCM (20 ml), then acidified and extracted with DCM (50 ml). The organic layer was washed with water (20 ml) and brine (20 ml), dried and evaporated. The residue was dissolved in dry DCM (10 ml) and oxalyl chloride (130 mg) was added, followed by one drop of DMF. The solution was stirred for 2 h, evaporated *in vacuo* and azeotroped to dryness. The residue was dissolved in THF (10 ml) and aqueous hydroxylamine (0.5 ml) added, the solution stirred for 2 h, diluted with water (20 ml) and evaporated to remove THF. The solid product was collected by filtration and washed with hexane-MTBE (10 ml) to give the title compound as a white solid (151 mg). MS 385 (M + H). 1H NMR (δH, $CDCl_3$) 8.5 (2H, br s), 7.15-7.3 (2H, m), 7.0 (1H, t), 6.9 (1H, d), 3.8-3.9 (2H, m), 3.85 (3H, s), 3.6 (1H, dd), 3.0 (1H, m), 2.95 (1H, dd), 2.8-2.9 (2H, m), 2.5 (1H, m), 1.7-2.0 (5H, m), 1.0 (6H, appears as triplet)

Similarly prepared using Method B were:

Example 14

2(*R*)-[4-(2-Methylphenyl)piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4-(2-methylphenyl)piperidine (170 mg) and 4(R)-benzyl-3-(2(R)-chlorosulfonylmethyl-3-methylbutyryl)oxazolidin-2-one (370 mg) as a white solid (16 mg). MS 369 (M + H). 1H NMR (δH, d_6DMSO) 10.7 (1H, s), 9.0 (1H, s), 7.1-

7.4 (4H, m), 3.7-3.9 (2H, m), 3.5 (1H, dd), 3.1 (1H, dd), 2.8-3.0 (3H, m), 2.5 (1H, m), 2.3 (3H, s), 1.6-1.9 (5H, m), 0.95 (6H, appears as doublet).

Example 15

2(*R*)-[4-(2-Fluorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide

Prepared from 4(R)-benzyl-3-(2(R)-chlorosulfonylmethyl-3-methylbutyryl)oxazolidin-2-one (180 mg) and 4-(2-fluorophenyl)piperidine (100 mg) as a beige solid (45 mg). MS 373 (M + H). 1H NMR (δH, d_6DMSO) 10.7 (1H, s), 8.9 (1H, s), 7.1-7.5 (4H, m), 3.6-3.8 (2H, m), 3.5 (1H, dd), 3.1 (1H, dd), 2.8-3.0 (3H, m), 2.4 (1H, dt), 1.6-1.9 (5H, m), 0.96 (6H, appears as doublet)

Method C

Example 16

1-[4-(2-Methoxyphenyl)-piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide

4-(2-Methoxyphenyl)piperidine (230 mg) was added to a solution of 1-(chlorosulfonylmethyl)cyclobutane carboxylic acid ethyl ester (240 mg) and triethylamine (200 mg) in DCM (20 ml) and the solution stirred at room temperature for 3 h, then washed with water (20 ml) and brine (20 ml), dried and evaporated. The residue was dissolved in methanol (20 ml) and a solution of lithium hydroxide (100 mg) in water (20 ml) was added. The solution was stirred overnight, then evaporated to half volume, acidified with 1M HCl and the mixture extracted with DCM (20 ml). The solvent was washed with water (20 ml) and brine (20 ml), dried and evaporated. The residue was dissolved in DCM (20 ml) and oxalyl chloride (200 mg) added, followed by one drop of DMF. The mixture was stirred for three hours, evaporated and azeotroped to dryness. The residue was dissolved in THF (20 ml) and aqueous hydroxylamine (0.5 ml) was added, the solution stirred for 3 h, then evaporated *in vacuo*, the residue triturated with water (10 ml) and the solid product collected by filtration to give the title compound as a white solid (64 mg). MS 383 (M + H). 1H NMR (δH, $CDCl_3$) 8.5 (2H, m), 7.1-7.3 (2H, m), 6.8-7.0 (2H, m), 3.9 (2H, m), 3.8 (3H, s), 3.5 (2H, s), 3.1 (1H, m), 2.8 (2H, m), 2.35 (2H, m), 2.25 (2H, m), 2.0 (2H, m), 1.7-1.9 (4H, m).

Similarly prepared using Method C was:

Example 17

1-[4-(2-Methylphenyl)piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide

From 1-(chlorosulfonylmethyl)cyclobutane carboxylic acid ethyl ester (100 mg) and 4-(2-methylphenyl)piperidine (100 mg) to give the title compound as a white solid (7.3 mg). MS 367 (M + 1). 1H NMR (δH, D_6DMSO) 10.5 (1H, s), 8.7 (1H, s), 7.0-7.2 (4H, m), 3.5 (2H, m), 3.4 (2H, s), 2.7 (3H, m), 2.1-2.5 (6H, m), 2.2 (3H, s), 1.5-1.8 (4H, m)

The ability of the compounds of the invention to inhibit the shedding of CD23 may be determined using the following assays:

Abbreviatons used:

DTT	Dithiothreitol	CO_2	Carbon Dioxide
FCS	Foetal Calf Serum	IL-4	Interleukin-4
ELISA	Enzyme Linked ImmunoSorbent Assay		

Plasma Membrane CD23 Shedding Assay

Plasma membranes were isolated from RPMI8866 cells by initally resuspending the cells in 20mM Hepes buffer (+ NaCl 150nM, $MgCl_2$ 1.5mM at pH 7.5 containing DTT 1mM) and homogenising in a glass Dounce homogeniser followed by centrifugation (500g for 5mins at 4°C) and removal of the supernatant. The homgenisation step was subsequently repeated twice on the remaining cell pellet in order to maximise the yield of membranes. Supernantants were then pooled, further centrifuged (48,000g for 60mins at 4°C) and finally resuspended in 1mM sodium bicarbonate. Plasma membranes were further enriched using an aqueous extraction method (Morre DJ & Morre DM 1989; BioTechniques 7; 9; 946-958).

Plasma membranes were incubated at 37°C in the presence and absence of inhibitor for 2 hours (Marolewski *et al* 1998; Biochem. J.; 333; 573-579) following which time the reaction was stopped by the addition of 100µM

Marimastat. Soluble CD23 shed from the plasma membranes was filtered through a 0.22μm Millipore filter plate and quantitated by ELISA. IC_{50} values were calculated by plotting inhibitor concentration versus %inhibition.

The functional effect of the compounds of the invention may be demonstrated using the following assays:

Cellular CD23 Shedding Assay

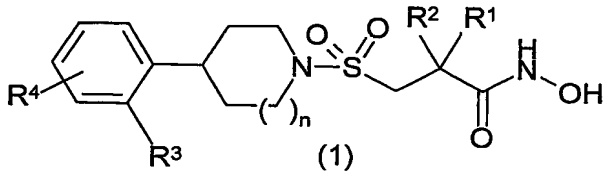
The RPMI8866 cell line is routinely grown in RPMI1640 medium containing 10% FCS but were washed twice and resuspended in serum-free RPMI1640 medium immediately prior to the assay. Cells were then plated out in the presence and absence of inhibitor and incubated at 37°C in an atmosphere of 95% air/5% CO_2 for 1 hour (Christie *et al* 1997; Eur. J. Immunol.; 27; 3228-3235). Following the time allocated, plates were centrifuged, the supernatants removed and subsequently analysed for shed soluble CD23 by ELISA. IC_{50} values were calculated by plotting inhibitor concentration versus %inhibition

***In Vitro* Human IgE Synthesis**

Mononuclear cells were isolated from human tonsillar tissue over a ficol gradient, washed in PBS and resuspended in RPMI1640 medium containing 10% FCS. Cells were then plated out, stimulated with 20ng/ml IL-4 / 5μg/ml anti-CD40 and incubated in the presence and absence of inhibitor at 37°C in an atmosphere of 95% air/5% CO_2 for 14 days (Christie *et al* 1997; Eur. J. Immunol.; 27; 3228-3235). Following the time allocated, plates were centrifuged, the supernatants removed and subsequently analysed for human IgE by ELISA. IC_{50} values were calculated by plotting inhibitor concentration versus %inhibition.

CLAIMS

1. A compound of formula (1):



(1)

wherein:

n is zero or the integer 1;

R^1 is a group selected from C_{1-6}alkyl, aryl, heteroaryl, heterocycloalkyl, C_{3-6}cycloalkyl, -C_{1-6}alkylaryl, -C_{1-6}alkylheteroaryl, -C_{1-6}alkylheterocycloalkyl or -C_{1-6}alkylC_{3-6}cycloalkyl, in which each aryl or heteroaryl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^7, wherein each R^7 may be the same or different, and is an atom or group selected from F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy or –CN; and in which each alkyl, heterocycloalkyl and cycloalkyl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^8, wherein each R^8 may be the same or different, and is an atom or group selected from F, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, =O or =NOR^{10};

R^{10} is a hydrogen atom or a C_{1-3}alkyl group;

R^2 is a hydrogen atom;

or R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl group optionally substituted with 1, 2 or 3 substituents selected from the group R^9, wherein each R^9 may be the same or different, and is an atom or group selected from F, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, =O or =NOR^{10};

R^3 is an atom or group selected from F, Cl, Br, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkoxy, C_{1-3}haloalkoxy or –CN;

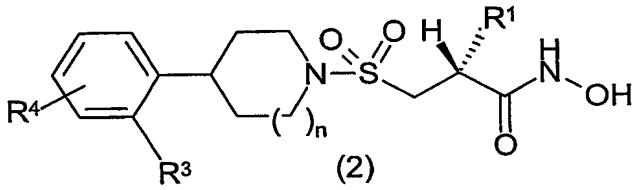
R^4 is a hydrogen, F, Cl or Br atom or a C_{1-3}alkyl, C_{1-3}haloalkyl, C_{1-3}alkoxy, C_{1-3}haloalkoxy, –CN, $-SO_2R^5$, $-SO_2N(R^6)_2$, $-CON(R^6)_2$, $-N(R^6)_2$, $-NSO_2R^5$ or $-NCOR^5$ group, in which each R^6 group may be the same or different;

R^5 is a C_{1-3}alkyl group;

R^6 is a hydrogen atom or a C_{1-3}alkyl group;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

2. A compound according to Claim 1 which has the formula (2):

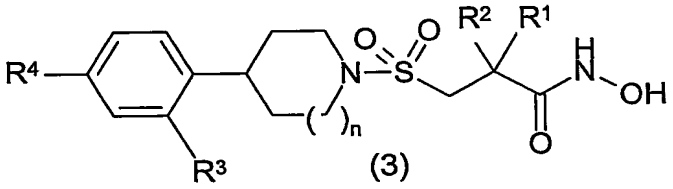


(2)

wherein n, R^1, R^2, R^3 and R^4 are as defined in Claim 1;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

3. A compound according to Claim 1 which has the formula (3):

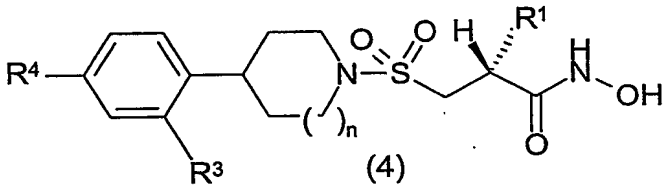


(3)

wherein n, R^1, R^3 and R^4 are as defined in Claim 1;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

4. A compound according to Claim 1 or 3 which has the formula (4):



(4)

wherein n, R^1, R^3 and R^4 are as defined in Claim 1;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

5. A compound of any preceding Claim in which n is the integer 1.

6. A compound of any preceding Claim in which R^1 is a group selected from C_{1-6}alkyl, phenyl, heteroaryl, heterocycloalkyl, C_{3-6} cycloalkyl, $-(CH_2)_{1-2}$phenyl, $-(CH_2)_{1-2}$heteroaryl, $-(CH_2)_{1-2}$heterocycloalkyl or $-(CH_2)_{1-2}C_{3-}$

$_{6}$cycloalkyl, in which each phenyl or heteroaryl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^7; and in which each alkyl, heterocycloalkyl and cycloalkyl group, present as or as part of the group R^1, may optionally be substituted with 1, 2 or 3 substituents selected from the group R^8.

7. A compound according to any preceding Claim in which R^1 is a group selected from optionally substituted C_{1-6}alkyl, phenyl, heterocycloalkyl, C_{3-6}cycloalkyl or $-(CH_2)_{1-2}$phenyl.

8. A compound according to Claims 1, 3 or 5 in which R^1 and R^2 together with the carbon atom to which they are attached form a C_{3-6} cycloalkyl group optionally substituted with 1, 2 or 3 substituents selected from the group R^9

9. A compound according to Claim 8 in which R^1 and R^2 together with the carbon atom to which they are attached form a cyclobutyl group.

10. A compound according to any preceding Claim in which R^3 is an atom or group selected from F, Cl, methyl, ethyl, i-propyl, $-CF_3$, $-CF_2H$, methoxy, ethoxy, $-OCF_3$, $-OCF_2H$ or –CN.

11. A compound according to any preceding Claim in which R^4 is an atom or group selected from hydrogen, F or Cl atom or a methyl, $-CF_3$, methoxy or $-OCF_2H$.

12. A compound of any preceding Claim wherein R^3 is an atom or group selected from F, Cl, C_{1-3}alkyl or C_{1-3}alkoxy.

13. A compound according to Claim 12 wherein R^3 is a C_{1-3} alkyl or C_{1-3}alkoxy group.

14. A compound according to Claim 12 or 13 wherein R^3 is a methyl or methoxy group.

15. A compound which is:

2-[4-(2-methoxyphenyl)piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide;

2-[4-(2-methyl-4-fluorophenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide;

2-benzyl-N-Hydroxy-3-[4-(2-methoxyphenyl)-piperidine-1-sulfonyl] propionamide;

2-benzyl-N-hydroxy-3-[4-(2-methylphenyl)-piperidine-1-sulfonyl] propionamide;

N-hydroxy-3-(4-(2-methoxyphenyl)-piperidine-1-sulfonyl]-2-phenyl propionamide;

2(*R*)-[4-(2-methoxyphenyl)-piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide;

2(*R*)-[4-(2-methylphenyl)piperidine-1-sulfonylmethyl]N-hydroxy-3-methylbutyramide;

1-[4-(2-methoxyphenyl)-piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide;

1-[4-(2-methylphenyl)piperidine-1-sulfonylmethyl]cyclobutane carboxylic acid hydroxyamide;

and the salts, solvates, hydrates, tautomers, isomers or N-oxides thereof.

16. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

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